Frontotemporal Lobar Degeneration: Clinical Syndromes, Molecular Pathogenesis, Neuroimaging, and Diagnostic Frameworks

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Abstract

Background:Frontotemporal lobar degeneration (FTLD) represents a heterogeneous group of neurodegenerative disorders characterized by progressive dysfunction in behavior, executive function, and language associated with selective degeneration of frontal and temporal networks. Increasing recognition of molecular heterogeneity and clinicopathological dissociation has reshaped contemporary understanding of FTLD.

Objective: To provide a comprehensive, high-level synthesis of FTLD integrating clinical phenotypes, molecular mechanisms, genetic architecture, and neuroimaging correlates, with emphasis on advances from 2020 to 2026.

Methods: A structured narrative review was conducted, emphasizing recent literature alongside foundational studies. Evidence was synthesized across clinical, genetic, neuropathological, and neuroimaging domains to construct an integrated disease framework.

Results: FTLD encompasses multiple clinical syndromes, including behavioural variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) variants, underpinned by distinct proteinopathies (tau, TDP-43, FUS). enetic discoveries, particularly involving MAPT, GRN, and C9orf72 have clarified disease mechanisms but also highlighted phenotypic variability. Neuroimaging and biomarker advances have improved diagnostic precision, although substantial clinicopathological discordance persists.

Conclusions: FTLD is best conceptualized as a network-based neurodegenerative spectrum driven by molecularly distinct but clinically overlapping processes. Future diagnostic and therapeutic strategies will depend on biomarker integration and molecular stratification.

Key words:
Frontotemporal Lobar Degeneration,
Clinical Syndromes, Molecular Pathogenesis,
Neuroimaging, and Diagnostic Frameworks

Overview: Nosology, Conceptual Framework, and Evolving Classification of FTLD

Frontotemporal lobar degeneration (FTLD) constitutes a major category of neurodegenerative disease defined by progressive degeneration of frontal and anterior temporal cortices, leading to impairments in behaviour, executive function, and language (Bang et al., 2015; Knopman et al., 2021). The distinction between frontotemporal dementia (FTD) as a clinical syndrome and FTLD as a pathological construct remains central, reflecting the divergence between phenotype and underlying molecular substrate (Kirshner, 2022).

Contemporary models emphasize FTLD as a network-based neurodegenerative disorder, wherein selective vulnerability of large-scale neural networks, particularly the salience network, semantic network, and language networks, drives clinical expression (Seeley et al., 2008; Zhou et al., 2012). This network degeneration paradigm explains the relative preservation of other cognitive domains in early disease stages and the progressive convergence of syndromes over time.

A critical evolution in FTLD research has been the recognition of clinicopathological dissociation, whereby identical clinical syndromes may arise from different molecular pathologies, and conversely, identical proteinopathies may produce divergent phenotypes depending on their anatomical distribution (Irwin et al., 2015; Negro et al., 2026). This has shifted the field from a purely syndromic classification toward a multidimensional framework integrating clinical, molecular, and imaging data.

Recent consensus frameworks further stratify FTLD into proteinopathy-based categories, primarily FTLD-tau, FTLD-TDP, and FTLD-FUS, each associated with distinct genetic and pathological signatures (Mackenzie et al., 2010; Neumann et al., 2006). Importantly, these molecular classifications do not map directly onto clinical syndromes, reinforcing the complexity of diagnosis and management.

Table 1: Clinical and pathological classification of FTLD syndromes

Clinical Syndrome	Core Features	Predominant Regions	Common Pathology
bvFTD	Behavioural disinhibition, apathy, executive dysfunction	Frontal (orbitofrontal, anterior cingulate, insula)	FTLD-TDP, FTLD-tau
nfvPPA	Agrammatism, apraxia of speech	Left frontal operculum, insula	FTLD-tau
svPPA (Semantic dementia)	Loss of semantic knowledge	Anterior temporal lobes	FTLD-TDP
lvPPA	Word-finding pauses, repetition deficits	Temporoparietal junction	Alzheimer pathology
FTLD-ALS	Behavioural + motor neurone disease	Frontal cortex, motor system	FTLD-TDP (C9orf72)

Source: Adapted from Gorno-Tempini et al. (2011); Rascovsky et al. (2011); Mackenzie et al. (2010)

Etiology: Molecular Mechanisms and Proteinopathies in FTLD

FTLD pathogenesis is fundamentally driven by abnormal protein aggregation and impaired proteostasis, leading to synaptic dysfunction, neuronal loss, and network-level degeneration (Bang et al., 2015; Rohrer & Warren, 2011). Unlike Alzheimer disease, which is dominated by amyloid-β and tau pathology, FTLD encompasses multiple distinct proteinopathies with overlapping but non-identical mechanisms.

1 Major Proteinopathies

FTLD-TDP

TDP-43 proteinopathy represents the most common pathological substrate in FTLD, accounting for approximately 50% of cases (Mackenzie et al., 2010). TDP-43 is a nuclear RNA-binding protein that regulates RNA splicing, transport, and stability. Pathological processes include:

- Cytoplasmic aggregation
- Nuclear depletion
- Post-translational modifications (phosphorylation, ubiquitination)

These changes result in both loss of normal nuclear function and toxic cytoplasmic gain-of-function, disrupting RNA metabolism and neuronal homeostasis (Ling et al., 2013; Neumann et al., 2006).

Recent studies have further classified FTLD-TDP into subtypes (A–E), each associated with specific clinical phenotypes and genetic mutations, particularly GRN and C9orf72 (Mackenzie et al., 2011; Irwin et al., 2015).

FTLD-Tau
Tauopathies in FTLD involve abnormal aggregation of hyperphosphorylated tau protein, leading to microtubule destabilization and impaired axonal transport (Spillantini & Goedert, 2013). Distinct tau isoforms (3R vs 4R) underlie different pathological entities, including Pick disease, corticobasal degeneration, and progressive supranuclear palsy (Lee et al., 2001).

Tau pathology is particularly associated with nonfluent PPA and Parkinsonian syndromes, reflecting involvement of frontal and motor networks (Grossman, 2010).

FTLD-FUS
FUS proteinopathies represent a smaller subset of FTLD but are notable for their early onset and severe behavioural phenotype (Urwin et al., 2010). FUS plays a role in RNA processing, and its aggregation further reinforces the central role of RNA dysregulation in FTLD.

Table 2. Major molecular proteinopathies in FTLD

Proteinopathy	Protein	Key Mechanism	Associated Syndromes
FTLD-TDP	TDP-43	RNA dysregulation, cytoplasmic aggregation	bvFTD, svPPA, FTLD-ALS
FTLD-tau	Tau	Microtubule dysfunction, aggregation	nfvPPA, PSP, CBD
FTLD-FUS	FUS	RNA processing impairment	Early-onset bvFTD

Source: Mackenzie et al. (2010); Neumann et al. (2006); Urwin et al. (2010)

2 Pathobiological Cascades

Emerging evidence suggests that FTLD pathogenesis involves interconnected molecular cascades, including:

- Impaired autophagy and proteasomal degradation
- Mitochondrial dysfunction
- Neuroinflammation
- Synaptic failure

TDP-43 aggregation, in particular, has been shown to propagate in a prion-like manner, facilitating trans-synaptic spread of pathology (Porta et al., 2018). Similarly, tau pathology demonstrates network-based propagation consistent with disease progression patterns observed clinically.

3 Network-Based Degeneration

Selective vulnerability of specific neural networks is a defining feature of FTLD. The salience network, anchored in the anterior insula and anterior cingulate cortex, is particularly affected in bvFTD, whereas language networks involving the left perisylvian and temporal regions are targeted in PPA variants (Seeley et al., 2008; Zhou et al., 2012).

Importantly, recent clinicopathological studies emphasize that anatomical distribution of pathology may be more predictive of clinical phenotype than molecular subtype, highlighting the importance of network-level analysis (Negro et al., 2026).

Genetic Distribution and Variation: Molecular Genetics and Genotype–Phenotype Relationships

Genetic factors play a critical role in FTLD, with approximately 30–50% of cases demonstrating familial aggregation and up to 40% exhibiting autosomal dominant inheritance (Rohrer et al., 2009; Goldman et al., 2005). Advances in molecular genetics have identified key pathogenic mutations that converge on common neurodegenerative pathways.

1 Major Genes

MAPT
MAPT mutations result in altered tau splicing and aggregation, leading to FTLD-tau pathology (Hutton et al., 1998). These mutations are associated with early-onset disease and often present with bvFTD or Parkinsonism.

GRN
GRN mutations cause progranulin haploinsufficiency, leading to TDP-43 pathology and increased neuroinflammation (Baker et al., 2006; Cruts et al., 2006). Clinically, GRN mutations are associated with asymmetric cortical atrophy and language-dominant presentations.

C9orf72
Hexanucleotide repeat expansions in C9orf72 represent the most common genetic cause of FTLD and are strongly linked to the FTLD-ALS spectrum (DeJesus-Hernandez et al., 2011; Renton et al., 2011). These expansions produce toxic RNA foci and dipeptide repeat proteins, contributing to neurodegeneration.

2 Additional Genetic Contributors
Emerging genes include:
- TBK1 (autophagy regulation)
- VCP (protein degradation pathways)
- CHMP2B (endosomal trafficking)
- FUS (RNA metabolism)

These genes highlight the central role of proteostasis and RNA regulation in FTLD pathogenesis (van der Zee et al., 2011).

3 Genotype–Phenotype Complexity
Although certain genotype–phenotype correlations exist, substantial variability remains. For example, C9orf72 mutations may present with bvFTD, ALS, or mixed phenotypes, while GRN mutations often produce asymmetric cortical degeneration (Rohrer et al., 2015).

This variability underscores the concept that genetic mutations influence disease biology but do not rigidly determine clinical phenotype, reinforcing the need for integrated diagnostic approaches.

Epidemiology: Global Burden and Demographic Patterns

FTLD is a leading cause of early-onset dementia, accounting for approximately 10–20% of cases in individuals under 65 years (Ratnavalli et al., 2002; Onyike & Diehl-Schmid, 2013). Prevalence estimates range from 5 to 15 per 100,000 individuals, although underdiagnosis remains a significant issue (Knopman & Roberts, 2011).

The disease typically presents between ages 45 and 65, although both earlier and later onset cases are well documented (Rabinovici & Miller, 2010). Sex distribution varies by subtype, with some evidence suggesting male predominance in bvFTD (Seelaar et al., 2011).

Prognosis: Disease Trajectory and Determinants of Outcome

FTLD is associated with progressive functional decline and reduced survival, with median survival ranging from 6 to 11 years from symptom onset (Onyike & Diehl-Schmid, 2013). Prognosis varies by subtype, with bvFTD often demonstrating more rapid progression compared to semantic dementia (Rabinovici & Miller, 2010).

The presence of motor neurone disease significantly worsens prognosis, with shorter survival observed in FTLD-ALS (Lomen-Hoerth et al., 2002). Additional prognostic factors include genetic mutations, extent of cortical involvement, and severity of executive dysfunction.

Clinical Syndromes of Frontotemporal Lobar Degeneration: Phenotypic Spectrum and Network-Based Correlates

Frontotemporal lobar degeneration is clinically expressed through a spectrum of syndromes that reflect selective degeneration of distributed neural networks rather than discrete anatomical lesions. Contemporary frameworks emphasize that these syndromes are best understood as network-driven phenotypes, with clinical manifestations emerging from disruption of large-scale functional systems, including the salience, semantic, and language networks (Seeley et al., 2008; Zhou et al., 2012).

Although categorized into behavioural and language-dominant syndromes, overlap is common, and longitudinal evolution frequently leads to convergence of phenotypes, reinforcing the concept of FTLD as a dynamic neurodegenerative continuum rather than a set of discrete disorders (Bang et al., 2015; Irwin et al., 2015).

1 Behavioural Variant Frontotemporal Dementia (bvFTD): Neurobehavioural Syndrome and Network Disintegration

Behavioural variant frontotemporal dementia represents the most prevalent clinical phenotype of FTLD and is characterized by early and progressive alterations in personality, social conduct, and executive function (Rascovsky et al., 2011; Bang et al., 2015). The syndrome reflects degeneration of frontal-insular networks that subserve emotional processing, decision-making, and social cognition.

1.1 Core Behavioural Domains

The diagnostic criteria for bvFTD emphasize six core behavioural domains, each reflecting disruption of specific neural circuits (Rascovsky et al., 2011):

1. Behavioural disinhibition
2. Apathy or inertia
3. Loss of empathy or sympathy
4. Perseverative, stereotyped, or compulsive behaviours
5. Hyperorality and dietary changes
6. Executive dysfunction with relative sparing of memory and visuospatial skills

These domains are not merely descriptive but correspond to dysfunction in distinct neuroanatomical substrates, particularly within the orbitofrontal cortex, anterior cingulate cortex, and anterior insula (Seeley et al., 2008).

Behavioural disinhibition arises from orbitofrontal dysfunction and is characterized by impulsivity, socially inappropriate behaviour, and impaired judgement. In contrast, apathy reflects medial frontal and anterior cingulate degeneration, resulting in reduced motivation and goal-directed behaviour (Rosen et al., 2005).

Loss of empathy represents a critical and often early feature, associated with degeneration of the anterior insula and limbic structures, leading to impaired emotional resonance and social awareness (Rankin et al., 2006).

1.2 Executive Dysfunction and Cognitive Profile

Executive dysfunction in bvFTD reflects impairment in frontal-subcortical circuits and manifests as deficits in planning, cognitive flexibility, response inhibition, and abstract reasoning (Perry & Hodges, 2000). Unlike Alzheimer disease, episodic memory may be relatively preserved in early stages, although subtle deficits in retrieval and organization may be present (Hornberger et al., 2008).

Importantly, traditional cognitive screening tools such as the Mini-Mental State Examination may underestimate impairment in bvFTD due to their limited sensitivity to executive dysfunction and social cognition deficits (Kipps et al., 2007).

1.3 Neuroanatomical and Network Correlates

The neuroanatomical substrate of bvFTD is centered on the salience network, which integrates emotional and cognitive information to guide behaviour (Seeley et al., 2008). Key nodes include:

- Anterior insula
- Anterior cingulate cortex
- Orbitofrontal cortex
- Ventromedial prefrontal cortex

Degeneration within this network disrupts the ability to evaluate emotional salience and regulate behaviour accordingly. Functional imaging studies demonstrate reduced connectivity within this network, correlating with behavioural severity (Zhou et al., 2012).

1.4 Pathological and Genetic Associations

bvFTD is associated with multiple underlying pathologies, most commonly FTLD-TDP and FTLD-tau (Mackenzie et al., 2010). Genetic mutations, particularly in C9orf72, MAPT, and GRN, are frequently observed and contribute to phenotypic variability (Rohrer et al., 2015).

C9orf72 expansions are often associated with prominent psychiatric features, including psychosis and behavioural dysregulation, highlighting the overlap between neurodegenerative and psychiatric disorders (Snowden et al., 2012).

1.5 Clinical Heterogeneity and Diagnostic Challenges

The heterogeneity of bvFTD poses significant diagnostic challenges, particularly in early stages when symptoms may mimic psychiatric conditions such as major depressive disorder, bipolar disorder, or personality disorders (Woolley et al., 2011). Misdiagnosis is common and contributes to delays in appropriate management.

Table 3. Core behavioural domains and neuroanatomical correlates in bvFTD

Behavioural Domain	Clinical Features	Neuroanatomical Correlates
Disinhibition	Impulsivity, socially inappropriate behaviour	Orbitofrontal cortex
Apathy	Reduced motivation, inertia	Anterior cingulate cortex
Loss of empathy	Emotional blunting, social insensitivity	Anterior insula
Compulsivity	Repetitive behaviours, rituals	Fronto-striatal circuits
Hyperorality	Dietary changes, overeating	Orbitofrontal-hypothalamic pathways
Executive dysfunction	Poor planning, cognitive rigidity	Dorsolateral prefrontal cortex

Source: Rascovsky et al. (2011); Seeley et al. (2008); Rosen et al. (2005)

2 Primary Progressive Aphasia: Language Network Degeneration and Variant-Specific Profiles

Primary progressive aphasia represents the language-dominant spectrum of FTLD and is defined by progressive impairment in language with relative preservation of other cognitive domains in early stages (Gorno-Tempini et al., 2011). The classification into three variants reflects distinct patterns of network degeneration within the language system.

2.1 Nonfluent/Agrammatic Variant (nfvPPA): Motor Speech and Syntax Network Degeneration

The nonfluent/agrammatic variant is characterized by impaired speech production and grammatical processing, reflecting degeneration of frontal language networks (Gorno-Tempini et al., 2011).

Clinical Features

- Effortful, halting speech
- Agrammatism
- Apraxia of speech
- Impaired comprehension of complex syntax

These deficits reflect disruption of neural circuits involved in motor planning and syntactic processing (Thompson et al., 2012).

Neuroanatomical Correlates

Atrophy is localized to:

- Left inferior frontal gyrus (Broca's area)
- Anterior insula
- Premotor cortex

These regions are critical for speech production and grammatical processing (Josephs et al., 2012).

Pathological Associations

nfvPPA is most commonly associated with FTLD-tau pathology, particularly corticobasal degeneration and progressive supranuclear palsy (Grossman, 2010).

2.2 Semantic Variant (svPPA / Semantic Dementia): Conceptual Knowledge Network Degeneration
Semantic dementia is characterized by progressive loss of semantic knowledge, affecting both language and conceptual understanding (Hodges & Patterson, 2007).

Clinical Features
- Severe anomia
- Impaired word comprehension
- Fluent but semantically empty speech
- Loss of object and person recognition

The impairment extends beyond language to encompass multimodal semantic memory, reflecting degeneration of conceptual knowledge systems.

Neuroanatomical Correlates
Degeneration predominantly affects:
- Anterior temporal lobes (left > right)

These regions function as a hub for semantic memory, integrating information across modalities (Patterson et al., 2007).

Right-sided involvement is associated with behavioural changes, including loss of empathy and social dysfunction, further illustrating overlap with bvFTD (Snowden et al., 2001).

Pathological Associations
Semantic dementia is strongly associated with FTLD-TDP type C pathology (Mackenzie et al., 2011).

2.3 Logopenic Variant (lvPPA): Phonological Network Disruption
The logopenic variant is characterized by impaired word retrieval and repetition, reflecting dysfunction of phonological processing networks (Gorno-Tempini et al., 2011).

Clinical Features
- Word-finding pauses
- Impaired sentence repetition
- Phonological errors
- Preserved grammar and articulation

Neuroanatomical Correlates
Atrophy involves:
- Left temporoparietal junction

This region supports phonological working memory and language integration (Rohrer et al., 2010).

Pathological Associations
Unlike other PPA variants, lvPPA is most commonly associated with Alzheimer disease pathology, highlighting the overlap between FTLD and Alzheimer spectrum disorders (Mesulam et al., 2008).

Table 4. Clinical, anatomical, and pathological features of PPA variants

Variant	Core Features	Neuroanatomical	Pathology
nfvPPA	Agrammatism, apraxia of speech	Left frontal operculum, insula	FTLD-tau
svPPA	Loss of semantic knowledge	Anterior temporal lobes	FTLD-TDP
lvPPA	Word-finding pauses, repetition deficits	Temporoparietal junction	Alzheimer pathology

Source: Gorno-Tempini et al. (2011); Mackenzie et al. (2011)

Behavioural Changes: Neuropsychiatric and Network-Level Mechanisms

Behavioural disturbances in FTLD reflect disruption of neural systems governing social cognition, reward processing, and emotional regulation. These changes are not merely secondary symptoms but represent core manifestations of network degeneration (Seeley et al., 2008).

1 Social Cognition and Theory of Mind
FTLD patients exhibit profound impairments in theory of mind and social cognition, including difficulty interpreting others' emotions and intentions (Rankin et al., 2006). These deficits are linked to degeneration of the anterior insula and medial prefrontal cortex.

2 Reward Processing and Eating Behaviour
Alterations in reward circuitry lead to hyperphagia, preference for sweet foods, and compulsive eating behaviours (Piguet et al., 2011). These changes are associated with orbitofrontal and hypothalamic dysfunction.

3 Compulsivity and Behavioural Rigidity
Repetitive behaviours and compulsions reflect dysfunction of fronto-striatal circuits and may resemble obsessive-compulsive disorder, although they are typically less anxiety-driven (Snowden et al., 2001).

4 Psychiatric Overlap and Misdiagnosis
Early FTLD frequently mimics psychiatric disorders, including depression, bipolar disorder, and schizophrenia, leading to diagnostic delays (Woolley et al., 2011). This overlap underscores the importance of integrating neurological and psychiatric evaluation.

Additional Presentations: Overlap Syndromes and Atypical Phenotypes in FTLD

Frontotemporal lobar degeneration extends beyond classical behavioural and language syndromes to include a spectrum of overlapping neurological conditions. These presentations reflect shared molecular mechanisms and network-level degeneration affecting motor, subcortical, and limbic systems (Bang et al., 2015; Irwin et al., 2015).

1 FTLD with Motor Neurone Disease (FTLD-ALS Spectrum)
The overlap between FTLD and amyotrophic lateral sclerosis (ALS) represents one of the most significant clinicopathological intersections in neurodegenerative disease. Approximately 10–15% of patients with FTLD develop motor neurone disease, while up to 50% of ALS patients demonstrate cognitive or behavioural impairment consistent with FTLD (Lomen-Hoerth et al., 2002; Phukan et al., 2007).

This overlap is strongly associated with TDP-43 pathology, particularly in the context of C9orf72 hexanucleotide repeat expansions, which represent the most common genetic cause of the FTLD-ALS spectrum (DeJesus-Hernandez et al., 2011; Renton et al., 2011).

Clinically, FTLD-ALS may present with:
- Behavioural changes preceding motor symptoms
- Concurrent cognitive and motor dysfunction
- Progressive weakness, fasciculations, and bulbar symptoms

The presence of ALS significantly worsens prognosis and accelerates disease progression (Olney et al., 2005).

2 Parkinsonian Syndromes Associated with FTLD
FTLD frequently overlaps with atypical Parkinsonian disorders, particularly:
- Progressive supranuclear palsy (PSP)
- Corticobasal syndrome (CBS)

These syndromes are typically associated with FTLD-tau pathology and may present with motor symptoms preceding or following cognitive impairment (Dickson et al., 2011).

Progressive Supranuclear Palsy (PSP)
Characterized by:
- Vertical gaze palsy
- Axial rigidity
- Postural instability
- Executive dysfunction

PSP reflects degeneration of subcortical and brainstem structures, including the midbrain and basal ganglia (Höglinger et al., 2017).

Corticobasal Syndrome (CBS)
Features include:
- Asymmetric rigidity and dystonia
- Limb apraxia
- Alien limb phenomenon
- Cortical sensory deficits

CBS is associated with widespread cortical and subcortical degeneration and demonstrates significant clinicopathological heterogeneity (Armstrong et al., 2013).

3 Right Temporal Variant FTLD
Right temporal lobe degeneration produces a distinct clinical phenotype characterized by:
- Loss of empathy
- Emotional blunting
- Prosopagnosia
- Behavioural rigidity

This variant highlights the role of the right anterior temporal lobe in social and emotional processing and often overlaps clinically with bvFTD (Snowden et al., 2001; Chan et al., 2009).

4 Mixed and Atypical Pathologies
Recent neuropathological studies emphasize the frequent coexistence of multiple proteinopathies within the same patient, including combinations of FTLD-TDP, tau, amyloid-β, and α-synuclein (Negro et al., 2026; Robinson et al., 2018).

These mixed pathologies contribute to:
- Atypical clinical presentations
- Diagnostic uncertainty
- Variability in disease progression

Importantly, such findings reinforce that clinical phenotype alone is insufficient to determine underlying pathology, underscoring the need for biomarker-based approaches.

Physical Examination: Neurological and Behavioural Assessment

Physical examination in FTLD extends beyond standard neurological assessment to include detailed evaluation of behaviour, executive function, and social cognition. Findings vary depending on the clinical subtype and disease stage.

1 General Neurological Findings
Early in the disease course, neurological examination may be relatively normal, particularly in bvFTD. However, as disease progresses, findings may include:
- Frontal release signs (grasp reflex, palmomental reflex)
- Primitive reflexes
- Motor abnormalities

These signs reflect frontal lobe dysfunction and disinhibition of primitive motor pathways (Perry & Hodges, 2000).

2 Motor System Examination
Motor findings are particularly relevant in overlap syndromes:
- Upper and lower motor neurone signs (FTLD-ALS)
- Rigidity and bradykinesia (PSP, CBS)
- Apraxia and dystonia (CBS)

Bulbar dysfunction, including dysarthria and dysphagia, may occur in advanced stages or in association with ALS (Phukan et al., 2007).

3 Behavioural and Cognitive Bedside Assessment
Bedside evaluation should include:
- Assessment of social appropriateness
- Emotional responsiveness
- Insight and judgement
- Language function

Loss of insight (anosognosia) is a hallmark feature of bvFTD and contributes significantly to caregiver burden (Hornberger et al., 2012).

Differential Diagnosis: Analytical Framework and Diagnostic Pitfalls

Differentiating FTLD from other neurodegenerative and psychiatric disorders remains a major clinical challenge due to overlapping symptoms and heterogeneous presentations.

1 Alzheimer Disease
Alzheimer disease is the most common differential diagnosis, particularly in early stages. Key distinguishing features include:
- Prominent episodic memory impairment in Alzheimer disease
- Early behavioural or language dysfunction in FTLD

However, overlap occurs, particularly in logopenic PPA, which is often associated with Alzheimer pathology (Mesulam et al., 2008).

2 Psychiatric Disorders
FTLD is frequently misdiagnosed as a primary psychiatric disorder, especially in younger patients. Common misdiagnoses include:
- Major depressive disorder
- Bipolar disorder
- Schizophrenia

Features suggesting FTLD rather than psychiatric illness include:
- Progressive course
- Loss of empathy
- Executive dysfunction
- Neurological signs

(Woolley et al., 2011)

3 Lewy Body Dementia and Parkinsonian Disorders
Differentiation from Lewy body dementia and Parkinson disease dementia is based on:
- Presence of hallucinations and REM sleep behaviour disorder (Lewy body dementia)
- Parkinsonian features preceding cognitive decline

(McKeith et al., 2017)

4 Vascular Dementia
Vascular dementia may mimic FTLD, particularly in cases with frontal-subcortical involvement. Neuroimaging is critical for differentiation (O'Brien & Thomas, 2015).

Table 5. Differential diagnosis of FTLD

Disorder	Key Features	Distinguishing Points
Alzheimer disease	Memory impairment	Early episodic memory loss
Psychiatric disorders	Mood/behavioural changes	Non-progressive, preserved cognition
Lewy body dementia	Hallucinations, Parkinsonism	Fluctuating cognition
Vascular dementia	Stepwise decline	Imaging evidence of vascular lesions

Source: Woolley et al. (2011); McKeith et al. (2017); Mesulam et al. (2008)

Laboratory and EEG Studies

Laboratory investigations in FTLD primarily serve to exclude reversible causes of cognitive impairment rather than to confirm diagnosis.

1 Laboratory Testing
Routine evaluation includes:
- Thyroid function tests
- Vitamin B12 levels
- Metabolic panel

Emerging biomarkers include:
- Neurofilament light chain (NfL)
- Progranulin levels

Elevated NfL levels have been associated with disease severity and progression in FTLD (Meeter et al., 2016).

2 EEG Findings
Electroencephalography is typically normal or shows nonspecific slowing in FTLD, contrasting with Alzheimer disease, where more pronounced abnormalities may be observed (Bonanni et al., 2008).

Language and Neuropsychological Testing: Domain-Specific Assessment

Neuropsychological evaluation is central to the diagnosis and characterization of FTLD, particularly in distinguishing between subtypes and differentiating from other dementias.

1 **Executive Function Assessment**
Tests include:
- Wisconsin Card Sorting Test
- Stroop Test
- Trail Making Test

These assessments reveal deficits in cognitive flexibility, inhibition, and planning, reflecting frontal lobe dysfunction (Perry & Hodges, 2000).

2 Language Assessment
Language testing is critical in PPA and includes:
- Naming tests (e.g., Boston Naming Test)
- Repetition tasks
- Comprehension assessments

Each PPA variant demonstrates a distinct profile, aiding in classification (Gorno-Tempini et al., 2011).

3 Social Cognition Testing
Assessment of social cognition includes:
- Theory of mind tasks
- Emotion recognition tests

These are particularly relevant in bvFTD and may detect deficits not captured by traditional cognitive tests (Rankin et al., 2006).

Table 6. Neuropsychological profiles across FTLD subtypes

Domain	bvFTD	nfvPPA	svPPA	lvPPA
Executive function	Severely impaired	Mild	Mild	Moderate
Language fluency	Reduced	Nonfluent	Fluent	Logopenic
Semantic knowledge	Mild	Preserved	Severely impaired	Mild
Memory	Partially preserved	Preserved	Preserved early	Impaired

Source: Gorno-Tempini et al. (2011); Perry & Hodges (2000)

Management: Evidence-Based Strategies and Multidimensional Care in FTLD

Management of frontotemporal lobar degeneration (FTLD) remains primarily symptomatic, reflecting the current absence of approved disease-modifying therapies. However, advances in understanding the neurobiology of FTLD have led to more targeted approaches addressing behavioural dysregulation, caregiver burden, and functional decline. Importantly, management must be multidisciplinary, incorporating pharmacologic, behavioural, and supportive interventions tailored to the dominant clinical phenotype and disease stage (Boxer & Boeve, 2007; Finger, 2016).

A key principle in FTLD management is that behavioural symptoms, not cognitive deficits, are often the primary drivers of disability and caregiver distress, particularly in behavioural variant FTD. Therefore, treatment strategies prioritize modulation of neuropsychiatric symptoms and environmental adaptation rather than cognitive enhancement (Bang et al., 2015; Olney et al., 2017).

1 Pharmacologic Management
Pharmacologic therapy in FTLD is largely extrapolated from neuropsychiatric and dementia literature, with limited randomized controlled trial evidence. Importantly, medication responses are variable, and inappropriate pharmacologic choices, particularly cholinergic agents, may exacerbate symptoms.

Core pharmacologic approaches include:
- Selective serotonin reuptake inhibitors (SSRIs)
  - Reduce disinhibition, compulsivity, irritability
  - May improve eating behaviours and emotional regulation
  - Common agents: sertraline, citalopram, fluoxetine
- Trazodone
  - Beneficial for agitation, irritability, and sleep disturbance
  - Evidence suggests improvement in behavioural symptoms
- Atypical antipsychotics (use with caution)
  - Indicated for severe agitation, aggression, or psychosis
  - Increased risk of cerebrovascular events and mortality
  - Agents: quetiapine, risperidone
- Stimulants (selected cases)
  - May improve apathy and executive dysfunction
  - Limited evidence; requires careful monitoring

- Avoidance of cholinesterase inhibitors and memantine
  - Generally ineffective in FTLD
  - May worsen behavioural symptoms in some patients

(Huey et al., 2006; Boxer & Boeve, 2007; Finger, 2016)

2 Non-Pharmacologic and Behavioural Interventions

Non-pharmacologic strategies represent the cornerstone of FTLD management, particularly given the limited efficacy of pharmacologic treatments. These interventions target environmental modification, behavioural reinforcement, and caregiver support.

Key interventions include:

- Structured daily routines
  - Reduce behavioural variability and anxiety
  - Enhance predictability and functional independence
- Behavioural modification strategies
  - Reinforcement of appropriate behaviours
  - Minimization of triggers for disinhibition or agitation
- Speech and language therapy (PPA variants)
  - Focus on compensatory communication strategies
  - Use of augmentative communication tools
- Occupational therapy
  - Adaptation of activities of daily living
  - Environmental safety modifications
- Caregiver education and support programs
  - Essential for reducing caregiver burden
  - Improve disease understanding and coping strategies

(O'Connor et al., 2016; Bang et al., 2015)

3 Management of Specific Clinical Domains

Given the heterogeneity of FTLD, symptom-targeted management is essential.

Behavioural symptoms

- SSRIs and trazodone as first-line agents
- Environmental modification to reduce triggers

Apathy

- Structured engagement strategies
- Consider stimulant therapy in selected patients

Language impairment (PPA)

- Speech therapy and communication aids
- Early intervention to preserve function

Motor symptoms (overlap syndromes)

- Parkinsonian features → limited response to dopaminergic therapy
- ALS features → multidisciplinary motor neurone disease care

4 Emergency and Acute Clinical Considerations in FTLD

Although FTLD is typically a chronic neurodegenerative condition, patients may present with acute or crisis situations that require urgent evaluation and intervention. These scenarios are often behavioural rather than neurological emergencies but carry significant risk to the patient and others.

Acute presentations frequently arise from severe disinhibition, aggression, impulsivity, or impaired judgement, reflecting frontal lobe dysfunction. Additionally, overlap with motor neurone disease may lead to acute respiratory or bulbar complications in advanced stages (Olney et al., 2005; Phukan et al., 2007).

Common emergency scenarios include:

- Severe behavioural dyscontrol
  - Aggression, violence, or socially dangerous behaviour
  - Immediate need for environmental control and pharmacologic sedation
- Psychiatric crises
  - Acute psychosis or severe agitation (especially in C9orf72-related disease)
  - May require short-term antipsychotic use
- Wandering and safety risks
  - Impaired judgement leading to hazardous situations
  - Requires supervision and environmental safeguards
- Nutritional complications
  - Hyperphagia or unsafe eating behaviours
  - Risk of aspiration or metabolic complications
- Bulbar or respiratory compromise (FTLD-ALS)
  - Dysphagia, aspiration pneumonia
  - Respiratory insufficiency requiring urgent support

Acute management principles:

- Ensure patient and caregiver safety first
- Use low-dose, short-term pharmacologic interventions when necessary
- Avoid over-sedation and polypharmacy
- Address underlying triggers (infection, environmental stressors)
- Consider hospitalization in severe cases

Future Directions: Toward Molecularly Targeted and Biomarker-Driven Therapies

The future of FTLD research is increasingly focused on precision medicine approaches, driven by advances in molecular biology, genetics, and biomarker development. A major paradigm shift is underway, from syndrome-based diagnosis to mechanism-based classification and treatment (Rohrer et al., 2020; Meeter et al., 2017).

Emerging therapeutic strategies aim to target the underlying molecular drivers of disease, including protein aggregation, RNA dysregulation, and neuroinflammation. These approaches are particularly promising in genetically defined forms of FTLD, where disease mechanisms are more clearly delineated.

Key future directions include:

1. Gene-targeted therapies

- Antisense oligonucleotides (ASOs) targeting C9orf72 repeat expansions
- Progranulin replacement strategies in GRN mutation carriers
- MAPT-targeted approaches for tauopathies

2. Protein-targeted therapies

- Tau aggregation inhibitors and anti-tau antibodies
- TDP-43 modulation strategies (currently experimental)

3. Biomarker development

- Fluid biomarkers (neurofilament light chain, progranulin levels)
- Imaging biomarkers (tau PET, advanced MRI techniques)
- Blood-based diagnostics for early detection

4. Network-based interventions

- Neuromodulation approaches targeting affected networks
- Non-invasive brain stimulation techniques

5. Clinical trial innovation

- Stratification based on genetic and molecular profiles
- Adaptive trial designs
- Earlier intervention in pre-symptomatic individuals

6. Digital and AI-based diagnostics

- Machine learning models for early detection
- Speech and behavioural analysis tools
- Wearable technologies for monitoring disease progression

Conclusion

Frontotemporal lobar degeneration (FTLD) represents one of the most complex and heterogeneous groups of neurodegenerative disorders, characterized by a striking dissociation between clinical phenotype, molecular pathology, and genetic architecture. The contemporary understanding of FTLD has evolved substantially from a purely syndromic framework toward an integrated, multidimensional model incorporating network degeneration, proteinopathy, and genetic drivers. This paradigm shift has clarified that clinical syndromes such as behavioural variant frontotemporal dementia and primary progressive aphasia are not discrete diseases but rather expressions of selective vulnerability within large-scale neural systems (Bang et al., 2015; Seeley et al., 2008).

A major challenge in FTLD remains the clinicopathological heterogeneity, whereby identical clinical presentations may arise from distinct molecular substrates, including TDP-43, tau, and FUS proteinopathies. This heterogeneity complicates diagnostic accuracy and limits the effectiveness of symptom-based classification systems. Increasing evidence suggests that anatomical distribution and network involvement may be more predictive of phenotype than molecular subtype, reinforcing the need for multimodal diagnostic approaches integrating imaging, genetics, and fluid biomarkers (Irwin et al., 2015; Negro et al., 2026).

Advances in neuroimaging have enabled more precise characterization of disease-specific atrophy patterns and network dysfunction, while molecular and genetic discoveries, particularly involving C9orf72, MAPT, and GRN, have provided critical insights into disease mechanisms. Nevertheless, despite these advances, therapeutic options remain limited, and current management strategies are largely symptomatic, focusing on behavioural control, supportive care, and caregiver interventions (Finger, 2016; Bartoshyk et al., 2025).

The future of FTLD research lies in the transition toward precision medicine, with an emphasis on early detection, molecular stratification, and targeted therapies. Emerging approaches, including antisense oligonucleotides, progranulin replacement, and tau-directed therapies, offer promising avenues for disease modification, particularly in genetically defined subgroups (Rohrer et al., 2020; Tartaglia et al., 2023). In parallel, advances in biomarker development and artificial intelligence-driven diagnostics are expected to enhance early diagnosis and improve clinical trial design (Dattola et al., 2025).

In summary, FTLD should be conceptualized as a biologically diverse, network-based neurodegenerative spectrum, requiring integrative diagnostic frameworks and individualized therapeutic strategies. Continued progress will depend on bridging the gap between molecular mechanisms and clinical expression, ultimately enabling disease-modifying interventions and improved patient outcomes

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